REMARKS

Upon entry of the present amendment, claims 1-3, 5, and 12-18 are pending. Claims 4, and 6-11 were previously cancelled without prejudice or disclaimer. Claim 1 has been amended. Applicants reserve the right to pursue cancelled subject matter in one or more continuing or divisional applications. No new matter has been added.

Double Patenting

Claims 1-3, 5, and 12-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over copending U.S. Patent Application Nos. (a) 11/081,002, (b) 11/602,307, and (c) 11/914,559. Applicant will consider filing a terminal disclaimer upon notice of allowable subject matter in these applications or the instant application.

Claim Rejection Under 35 U.S.C § 112

Claims 1-3, 5 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the Office Action states that the specification, while being enabling for a pharmaceutically acceptable salt or amino acid conjugate, does not provide enablement for a solvate. Applicant has amended claim 1 to delete ", solvates". Regarding the deletion, Applicant notes that a solvate, for example a hydrate, of a compound of formula (I) or a pharmaceutically acceptable salt thereof, would necessarily comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof, and infringe the claim. Claims 2 and 3 do not recite the term "solvates" and claims 5 and 12-18 properly depend from amended claim 1. Accordingly, Applicant submits that the rejection is now moot with respect to the amended claims and requests withdrawal of the rejection.

Claim Rejection Under 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 1-3, 5, and 12-18 under 35 U.S.C. § 103(a) over Frigerio et al. (EP 312,867) ("Frigerio") stating that Applicant's argument was considered but no persuasive. Applicant traverses the rejection.

The Office Action alleges that the present compound is obvious because the Examiner states that Frigerio teaches the adjacent lower homolog i.e., 6-methyl UDCA. Thus, the skilled artisan would have a reasonable expectation that extension of the 6-methyl substituent of the

UDCA derivative disclosed in Frigerio to 6-ethyl would predictably lead to compounds with similar properties. Further, the Office Action cites *In re Henze*, 85 USPQ 261, 263 and states that the court has held that adjacent homologs are obvious absent a showing of unexpected and obvious results. Applicant has not provided any evidence on record showing the claimed compound has an unexpected and/or obvious properties not possessed by the prior art compound.

Applicant maintains the assertion that a *prima facie* case of obviousness has not been established and reiterate their arguments presented in the papers filed on November 3, 2008 and July 13, 2009. Frigerio is fatally deficient. Frigerio does not disclose the presently claimed 6-alpha-**ethyl** substituted UDCA FXR agonists. Rather, Frigerio discloses 6-**methyl** UDCA derivatives having both the **alpha**- and **beta**-configurations at the 6-position with no mention of the 6-alpha configuration being preferred and further, Frigerio does not mention FXR activity, the superior property of the claimed invention. This is not surprising, as the FXR receptor was not discovered until 1999--12 years after Frigerio was filed and given that 6-methyl UDCA derivatives do not have significant FXR activity as discussed in more detail below.

Frigerio provides no teaching or suggestion (1) to select the 6-alpha methyl UDCA diastereomer and to then (2) extend the 6-methyl alpha substituted by an additional -CH_2- group to produce the claimed FXR agonist: 6-alpha-ethyl UDCA. Accordingly, Applicant submits that the skilled artisan reading Frigerio would not have arrived at the claimed FXR agonist with predictable results. A *prima facie* case of obviousness has not been established. Applicant requests withdrawal of the rejection.

Finally, in an effort to facilitate the more timely allowance of the case and in spite of a lack of prima facie case obviousness, a comparison of the FXR potency of the claimed compound to the prior art compounds, 6-methyl UDCA and UDCA, yields surprising and unexpected results--not possessed by the prior art compounds.

Applicant presents herein the declaration of Dr. Roberto Pellicciari ("the Declaration") which shows comparative FXR activity data for certain UDCA derivatives. Specifically, as described in the Declaration of Dr. Roberto Pellicciari pursuant to 37 C.F.R. § 1.132, submitted herewith, the 6-α-ethyl UDCA derivative exhibits the unexpected and surprising result of being a **significantly more potent** FXR ligand than other UDCA derivatives, including the 6-methyl UDCA derivatives of Frigerio. The claimed 6-α-ethyl UDCA derivatives possess an important

and previously unpredictable property as they are more potent than UDCA and Frigerio's 6-methyl UDCA compounds.

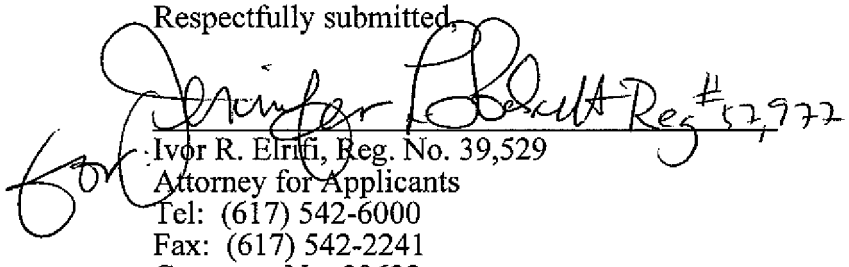
First, UDCA is known in the art to be essentially inactive on FXR. *See*, Table 1 of the Declaration; Pellicciari et al., Journal of Medicinal Chemistry, 2002 at page 3569, second column and also, Bramlett et al. Molecular Genetics and Metabolism 71, 609 (2000) which also states that UDCA is inactive (*See*, Bramlett, abstract, line 31)). Copies of these two references are provided as a courtesy to the Examiner. As such, the skilled artisan knowing that UDCA has no significant affinity for FXR would not be motivated to modify UDCA by adding an ethyl substituent at the 6-position of the steroid structure and further would not predict that addition of such a substituent would lead to a compound with FXR activity at all--let alone, superior FXR activity. Additionally, as shown in Table 1, the 6-α-methyl UDCA derivative of Frigerio also does not show significant affinity for FXR as it has an EC_{50} value of about 35 μM. Based on the lack of FXR activity for these two UDCA compounds, Applicants submit that the skilled artisan would not have been motivated to prepare the presently claimed 6-α-ethyl UDCA derivatives or have predicted the surprisingly good FXR activity of the claimed 6-α-ethyl UDCA derivatives. As shown in Table 1 of Dr. Pellicciari's Declaration, the 6-α-ethyl UDCA derivative is approximately **8 times more potent** as an FXR ligand than the corresponding 6-methyl compound. This significant increase in FXR potency for the claimed compound is unexpected and very desirable as it is likely to produce a more efficacious, active compound with fewer unwanted side effects.

The fact that 6-α-ethyl UDCA is a potent FXR ligand would not have been obvious to one skilled in the art based on Frigerio or the fact that it is explicitly stated in the prior art that UDCA is not a ligand for FXR. The 6-α–ethyl UDCA compounds of the present invention are neither taught nor suggested by Frigerio. Furthermore, 6-α-ethyl UDCA's potent FXR agonist activity is surprising and unexpected and FXR agonist activity is not taught or suggested by Frigerio. Therefore, the 6-α-ethyl UDCA derivatives of the present invention are not rendered obvious by Frigerio. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit, that the pending claims are in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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